LINEAR AND CYCLIC MELANOCORTIN RECEPTOR-SPECIFIC PEPTIDES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of International Patent Application Serial No. PCT/US02/22196, Publication No. WO 03/006620, entitled "Linear and Cyclic Melanocortin Receptor-Specific Peptides", filed on July 11, 2002, and the specification thereof is incorporated herein by reference.

This application claims the benefit of the filing of U.S. Provisional Patent Application Serial No. 60/304,836, entitled "Linear and Cyclic Melanocortin Receptor-Specific Peptides", filed on July 11, 2001, and the specification thereof is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Field of the Invention (Technical Field):

The present invention provides both linear and cyclic peptides that are specific for one or more melanocortin receptors, and which may be used in the treatment of a wide variety of diseases.

Background Art:

Melanocortin Receptors. A family of melanocortin receptor types and subtypes have been identified, including melanocortin-1 receptors (MC1-R) expressed on normal human melanocytes and melanoma cells, melanocortin-2 receptors (MC2-R) for ACTH (adrenocorticotropin) expressed in cells of the adrenal gland, melanocortin-3 and melanocortin-4 receptors (MC3-R and MC4-R) expressed primarily in cells in the hypothalamus, mid-brain and brainstem, and melanocortin-5 receptors (MC5-R), expressed in a wide distribution of peripheral tissues.

Peptides specific for melanocortin receptors have been reported to have a wide variety of biological activities, including effects upon pigmentation and steroidogenesis, known to be mediated by MSH (melanocyte stimulating hormone) and ACTH receptors. Several studies have documented the presence of melanotropin receptors on primary human melanoma cells (Tatro JB, Atkins M, Mier JW, et al. Melanotropin receptors demonstrated in situ in human melanoma. *J Clin Invest*, 85:1825-1832, 1990). Melanotropin receptors have been reported as markers for melanotic and amelanotic human melanoma tumors (Sharma SD, Granberry ME, Jiang J, et al. Multivalent melanotropic peptide and fluorescent macromolecular conjugates: new reagents for characterization of melanotropin receptors. *Bioconjug Chem* 5:591-601, 1994; Sharma SD, Jiang J, Hadley ME, et al. Melanotropic

peptide-conjugated beads for microscopic visualization and characterization of melanoma melanotropin receptors. *Proc Natl Acad Sci U S A* 93(24):13715-13720, 1996). In particular, the presence of MC1-R has been demonstrated in human melanoma cells by an antibody to MC1-R (Xia Y, Skoog V, Muceniece R, et al. Polyclonal antibodies against human melanocortin MC-1 receptor: Preliminary immunohistochemical localization of melanocortin MC1 receptor to malignant melanoma cells. *European J Pharmacol* 288:277-283, 1995). MC1-R is a G protein-coupled, 7-transmembrane receptor expressed in skin-cell melanocytes and shares some degree of homology with related receptors MC2-R, MC3-R, MC4-R and MC5-R. Each of these receptors can bind various peptide analogs that contain a common melanotropic pharmacophore, His-Phe-Arg-Trp (SEQ ID NO: 1), which describes the 6-9 sequence of the alpha-melanocyte stimulating hormone (α-MSH).

Prior to molecular characterization of the MC receptors, α-MSH analogs were labeled with the radioisotope Indium-111 and used in melanoma imaging studies (Wraight EP, Bard DR, Maughan TS, et al. The use of a chelating derivative of alpha melanocyte stimulating hormone for the clinical imaging of malignant melanoma. *Brit J Radiology* 65: 112-118, 1992; Bard DR, Knight CG and Page-Thomas DP. A chelating derivative of alpha-melanocyte stimulating hormone as a potential imaging agent for malignant melanoma. *Brit J Cancer* 62:919-922, 1990; Bard DR, Knight CG, Page-Thomas DP. Targeting of a chelating derivative of a short chain analogue of alpha-melanocyte stimulating hormone to Cloudman S91 melanomas. *Biochem Soc Trans* 18:882-883, 1990). Linear and cyclic disulfide-containing peptides have been identified and used for melanoma imaging and appear to be non-selective among MC receptors (Chen J and Quinn TP. Alpha melanocyte stimulating hormone analogues Tc-99m/Re-188 labeling and their pharmacokinetics in malignant melanoma bearing mice. *J Nucl Med* 39: 222p, 1998; Giblin MF, Wang N, Hoffman TJ, et al. Design and characterization of alpha-melanotropin peptide analogs cyclized through rhenium and technetium metal coordination. *Proc Natl Acad Sci U S A* 95(22):12814-12818, 1998). In later studies, the cyclic peptide reported by Giblin and coworkers was also found to localize in the brain (Wang NN, Giblin MF, Hoffman TJ, et al. In vivo characterization of Tc-99m and Re-188 labeled cyclic melanotropin peptide analogues in a murine melanoma model. *J Nucl Med* 39: 77p, 1998 and corresponding poster presentation at the 45th Society of Nuclear Medicine Meeting, Toronto, June 1998). It has been recently reported that the response of human melanocytes to UV radiation is mediated by α-MSH induced activation of the cAMP pathway through the MC1-R (Im S, Moro O, Peng F, et al. Activation of the cyclic AMP

pathway by alpha-melanotropin mediates the response of human melanocytes to ultraviolet B radiation. *Cancer Res* 58: 47-54, 1998).

MC4-R is also a G protein-coupled, 7-transmembrane receptor, but is believed to be expressed primarily in the brain. Inactivation of this receptor by gene targeting has been reported to result in mice with the maturity-onset obesity syndrome that is associated with hyperphagia, hyperinsulinemia, and hyperglycemia (Huszar D, Lynch CA, Fairchild-Huntress V, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell* 88:131-141, 1997). MC4-R is a molecular target for therapeutic intervention in energy homeostasis.

Alpha-MSH has been described as a potent anti-inflammatory agent in all major forms of inflammation (Star RA, Rajora N, Huang J, Stock RC, Catania A, and Lipton JM. Evidence of autocrine modulation of macrophage nitric oxide synthase by alpha-melanocyte stimulating hormone. *Proc Natl Acad Sci U S A* 92:8016-8020, 1995; Getting SJ, and Perretti M. MC3-R as a novel target for antiinflammatory therapy. *Drug News and Perspectives* 13:19-27, 2000). Implication of both MC1-R and MC3-R receptors in anti-inflammatory processes has been stressed. In particular, the activation of these MC receptors by melanocortin receptor agonists has been reported to inhibit the expression of nitric oxide synthase and subsequent nitric oxide production.

Significant work has been done in determining the structure of melanocortin receptors, including both the nucleic acid sequences encoding for the receptors and the amino acid sequences constituting the receptors. See, for example, International Patent Application Nos. PCT/US98/12098 and PCT/US99/16862 and U.S. Patent No. 5,994,087. A large number of ligands specific for melanocortin receptors, both agonists and antagonists, have also been developed. See, for example, International Patent Application Nos. PCT/US00/16396, commonly owned with this application and with common inventors (metallopeptides specific for MC receptors); PCT/US98/03298 (iodo group-containing melanocortin receptor-specific linear peptide); PCT/GB99/01388 (MC1-R specific linear peptides); PCT/GB99/01195 (MC3-R, MC4-R and MC5-R specific cyclic peptides); PCT/US99/04111 (MC1-R specific peptide antagonists for melanoma therapy); PCT/US99/09216 (isoquinoline compounds as melanocortin receptor ligands); PCT/US99/13252 (spiropiperdine derivatives as melanocortin receptor agonists); and U.S. Patent No. 6,054,556 (cyclic lactam peptides as MC1-R, MC3-R, MC4-R and MC5-R antagonists). In addition, a large number of patents teach various methods of screening and determining melanocortin receptor-specific compounds, as for example

International Patent Application Nos. PCT/US97/15565, PCT/US98/12098 and PCT/US99/16862 and U.S. Patent Nos. 5,932,779 and 5,994,087.

In general, compounds specific for MC1-R are believed to be useful for treatment of melanoma, including use as radiotherapeutic or drug delivery agent, and as diagnostic imaging agents, particularly when labeled with a diagnostic radionuclide. Compounds specific for MC3-R, MC4-R or MC5-R are believed to be useful in regulation of energy homeostasis, including use as agents for attenuating food intake and body weight gain, for use in treatment of anorexia, as a weight gain aid, for treatment of obesity, and other treatment of other food intake and metabolism-related purposes. Compounds specific for MC3-R and MC4-R, among other melanocortin receptors, can be used as agents for treatment of sexual dysfunction, including male erectile dysfunction. Compounds specific for MC3-R and MC4-R, among other melanocortin receptors, can be used to regulate blood pressure, heart rate and other neurophysiologic parameters. Other melanocortin receptor peptides can be used as tanning agents, to increase melanin production, such as peptides that are MC1-R agonists. Compounds specific for MC1-R and MC3-R may be useful in regulation of inflammatory processes.

There remains a significant need for ligands with high specificity for discrete melanocortin receptors, as well as ligands or compounds that are either agonists or antagonists of specific melanocortin receptors. High affinity peptide ligands of melanocortin receptors can be used to exploit varied physiological responses associated with the melanocortin receptors, either as agonists or antagonists. In addition, melanocortin receptors have an effect on the activity of various cytokines, and high affinity peptide ligands of melanocortin receptors can be used to regulate cytokine activity.

SUMMARY OF THE INVENTION (DISCLOSURE OF THE INVENTION)

In one embodiment the invention provides a peptide comprising the sequence $S_1 - S_2 - S_3 - S_4 - S_5$, wherein:

S_1 is any functionality that potentiates the intrinsic activity of the remainder of the peptide, including but not limited to providing an auxiliary or secondary receptor contact; including any of a variety of amino acids and non-peptide groups, including an amino acid chain from one to about four neutral or charged L- or D-configuration amino acid residues, and further wherein if S_1 is a non-peptide group, it comprises a linear or branched alkyl, aryl, alkene, alkenyl or aralkyl chain;

S_2 is absent, or if provided, a residue acting as a spacer, and preferably one or more natural or unnatural aliphatic amino acids, including Gly, Ala, Val, Leu or Nle, of either L- or D-configuration;

S_3 is L- or D- Phe, Phe(4-Cl), Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-NO_2), Phe(4-Me), Phe(4-Phenyl), Hphe, Pgl, Trp, Nal 1, Nal 2, Bip, Dip, Bpa, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl), Tyr($BzlCl_2$) or any natural or unnatural L- or D-amino acid with an aromatic side chain group, wherein the aromatic ring is optionally functionalized with halogen, alkyl or aryl groups;

S_4 is L- or D- Lys, Arg, Orn, Dpr, Dbu, p-amino-Phe or any natural or unnatural L- or D-amino acid with a positively charged side chain, and preferably an L-configuration cationic amino acid;

S_5 is an L- or D- amino acid with an aromatic side chain, and optionally comprising one or more additional amino acids, and further optionally comprising a terminus group, including Phe, Phe(4-Cl), Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-NO_2), Phe(4-Me), Phe(4-Phenyl), Hphe, Pgl, Trp, Nal 1, Nal 2, Bip, Dip, Bpa, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl), Tyr($BzlCl_2$), N-alkylated or arylated derivatives of any of the foregoing, or a des-carboxyl amino acid corresponding to any of the foregoing, in which event S_5 comprises a substituted amide function of the S_4 residue.

In yet another embodiment, the invention provides a peptide, comprising the sequence $S_1 - S_2$ – D-Phe(4-Cl) – $S_4 - S_5$, wherein:

S_1 is heptanoyl, 2'-naphthylacetyl, 7'-amino-heptanoyl, 2'-chlorophenylacetyl, 3'-chlorophenylacetyl, 4'-chlorophenylacetyl, 4'-phenylbutylaminocarbonyl, 3'-phenylbutylaminocarbonyl, 4'-bromophenyl-acetyl, 3-4-dichlorophenyl-acetyl, 2,4-dichlorophenyl-acetyl, 4-biphenyl-acetyl, 2-naphthoyl, Ph-$(CH_2)_2NH$, 3'-phenylpropanecarbonyl, 2'-naphthoyl-Pip, 2'-naphthylacetyl, 2'-bromophenyl-acetyl, 4'-CF_3phenyl-acetyl, 3'-CF_3phenyl-acetyl, 2'-CF_3phenyl-acetyl, 3',5'-CF_3phenylacetyl, 2',5'-CF_3phenylacetyl, 4'-Mephenyl-acetyl, 3'-Mephenyl-acetyl, 2'-Mephenyl-acetyl, 7'-aminoheptonoyl, beta-Ala, 4-aminoBytyl, 5-aminoValeryl, 6-aminoCaproyl, aminoTranexamyl, Cmpi or 3',4'-Cl_2phenylacetyl;

S_2 is absent or is Ser(Bzl), Ala, D-Ala, beta-Ala, Val, Leu, Chg, Aib, Tle, 1-amino-1cyclohexanecarbonyl, Inp, $CO(CH_2)_2NH$, $CO(CH_2)_2CO$, Pip, MeThr(Bzl), Thr(Bzl) or D-Thr(Bzl);

S_4 is Arg, D-Arg, (Nlys)Gly, Trp, Lys, homoLys, Dpr(beta-Ala), alpha-(N-amidino-4'-piperidine)Gly, (4'-guanidino)Gly, (4'-guanidino)Phe, D-(4'-guanidino)Phe, beta-(N-amidino-4'-peperidine)Ala or homo-Ala-4'-pip(N-amidino); and

S_5 is Trp, Trp-OH, Trp-NH_2, Trp-Cys-NH_2, D-Trp, D-Trp-NH_2, Trp-Val-NH_2, 3'-Pya-NH_2, Phe-NH_2, MeTrp-NH_2, beta-Ala-Trp-NH_2, aminobutylamide, Nal 1-NH_2, D-Nal 1-NH_2, Nal 2-NH_2, D-Nal 2-NH_2, Tic-NH_2, D-Tic-NH_2, 1'-aminoindan, 1'-aminoindane-1-carboxyl-NH_2, Aic-NH_2, Atc-NH_2, Disc-NH_2, Tpi-NH_2, D-Tpi-NH_2, Tiq-NH_2, D-Tiq-NH_2, tryptamide, NMe-tryptamide, alpha-Me-tryptamide, 2'-(4"-methylphenyl)ethylamide, 3',4'-Cl_2)phenylmethylamide, 3'-phenylpropylamide, 2',4'-dichlorobenzylamide, 3'-(1H-imidazol)propylamide, 4-phenyl-piperidine-4-carbonamide, 3-phenyl-1-propylamide, 2,4-dichlorophenethylamide, S-(-)-1-(2-naphthyl)ethylamide, S-(-)-1-(1-naphthyl)ethylamide, 2'-methylbenzylamide, 4'-methylbenzylamide, 2',2'-diphenylethylamide, 1-(2-pyridyl)piperazine, N-benzylmethylamide, histamide, R-(+)-1-(2-Naphthyl)ethylamide, Trp-Asp-NH_2, Trp-Asp-Phe-NH_2, Asp-Trp-NH_2, Ala-Trp-NH_2, Trp-Ala-NH_2, phenethylamide or Trp-Asp-OH.

Representative peptides of the formula $S_1 - S_2 -$ D-Phe(4-Cl) $- S_4 - S_5$ include 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-NH_2, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-Ala-NH_2, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-Asp-Phe-NH_2, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-Asp-NH_2, heptanoyl-Thr(Bzl)-D-Phe(4-Cl)-Arg-Trp-NH_2, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-MeTrp-NH_2, heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-MeTrp-NH_2, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Tryptamide, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-NMe-Tryptamide, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-alpha-Me-Tryptamide, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-S-(-)-1-(1-Naphthyl)ethylamide, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Nal 1-NH_2, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-D-Nal 2-NH_2, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Nal 2-NH_2, 2'-naphthylacetyl-Ala-D-Phe(4-Cl)-Arg-Trp-NH_2, 4'phenylbutyryl-Ala-D-Phe(4-Cl)-Arg-Trp-NH_2, 3',4'-dichlorophenyl-acetyl-Ala-D-Phe(4-Cl)-Arg-Trp-NH_2, and 3'-CF_3phenyl-acetyl-Ala-D-Phe(4-Cl)-Arg-Trp-NH_2.

In yet another embodiment, the invention provides a peptide comprising the sequence 7'-amino-heptanoyl $- S_2 -$ D-Phe(4-Cl) $- S_4 - S_5$, wherein S_2, S_4 and S_5 are as defined above. Peptides of the formula 7'-amino-heptanoyl $- S_2 -$ D-Phe(4-Cl) $- S_4 - S_5$ include each of the representative peptides of the preceding paragraph wherein the initial residue is 7'-amino-heptanoyl.

In yet another embodiment, the invention provides a peptide comprising the sequence $S_1 - S_2 - S_3 - S_4 - S_5$, wherein S_1, S_2, S_4 and S_5 are as defined above, and S_3 is Phe, D-Phe, Phe(4-Cl), D-Phe(4-Cl), Phe(3-Cl), D-Phe(3-Cl), Phe(2-Cl), D-Phe(2-Cl), D-Phe(3,4-diCl), MePhe, D-MePhe, D-Tic, D-Tpi, D-Nal 2, Arg, D-Phe(3,4-F_2), D-Tiq, D-Me(homo)Phe or D-EtPhe. Representative peptides of the formula $S_1 - S_2 - S_3 - S_4 - S_5$ include the foregoing described peptides and 7'-amino-heptanoyl-Ser(Bzl)-D-Nal 2-Arg-Trp-NH_2, 7'-amino-heptanoyl-Ala-D-Nal 2-Arg-Trp-NH_2, Ser(Bzl)-D-Nal 2-Arg-Trp-NH_2 and Ser(Bzl)-D-Nal 2-Arg-D-Trp-NH_2.

The invention further comprises a method for stimulating sexual response in a mammal, comprising administering a pharmaceutically sufficient amount of a composition comprising a peptide or pharmaceutically acceptable salt thereof. In this method, the mammal may be a male or a female. The composition may further comprise a pharmaceutically acceptable carrier. In the method, administering may include administering by a method of administration such as administration by injection, administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, nasal administration, parenteral administration, pulmonary administration, ocular administration, sublingual administration and vaginal adminstration. In the event of nasal administration, it may be nasal administration of a metered amount of a formulation comprising an aqueous buffer.

The invention further comprises a method for inhibiting food uptake in a mammal, comprising administering a pharmaceutically sufficient amount of a composition comprising a peptide or pharmaceutically acceptable salt thereof, and particularly an MC3/4-R selective agonist. The composition may further comprise a pharmaceutically acceptable carrier. In the method, administering may include administering by a method of administration such as administration by injection, administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, nasal administration, parenteral administration, pulmonary administration, ocular administration and sublingual administration. In the event of nasal administration, it may be nasal administration of a metered amount of a formulation comprising an aqueous buffer.

The invention further comprises a method for increasing weight gain in a mammal, comprising administering a pharmaceutically sufficient amount of a composition comprising a peptide or pharmaceutically acceptable salt thereof, and particularly an MC4/5-R selective antagonist. The composition may further comprise a pharmaceutically acceptable carrier. In the method,

administering may include administering by a method of administration such as administration by injection, administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, nasal administration, parenteral administration, pulmonary administration, ocular administration and sublingual administration. In the event of nasal administration, it may be nasal administration of a metered amount of a formulation comprising an aqueous buffer.

A primary object of the present invention is a melanocortin receptor-specific pharmaceutical for use in treatment of sexual dysfunction.

A second object is to provide a melanocortin receptor-specific pharmaceutical for use in treatment of male sexual dysfunction, including erectile dysfunction.

Another object is to provide a melanocortin receptor-specific pharmaceutical for use in treatment of female sexual dysfunction.

Another object is to provide a melanocortin receptor-specific pharmaceutical for use in treatment of eating disorders.

Another object is to provide a melanocortin receptor-specific pharmaceutical for use in treatment of which is effective by nasal administration.

Another object of this invention is to provide compounds which are specific for melanocortin receptors MC3-R and/or MC4-R and/or MC5-R and which are agonists or antagonists.

Other objects, advantages and novel features, and the further scope of applicability of the present invention, will be set forth in part in the detailed description to follow, taken in conjunction with the accompanying drawings, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of this invention. The objects and advantages of this invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated into and form a part of the specification, illustrate several embodiments of the present invention and, together with the description, serve to explain the principles of the invention. The drawings are only for the purpose of illustrating a preferred embodiment of the invention and are not to be construed as limiting the invention. In the drawings:

Fig. 1 is a graph of displacement of I^{125}-NDP-α-MSH bound to MC1-R, MC3-R, MC4-R and MC5-R using varying concentrations of 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-NH_2. The x-axis is percent 1^{125}-NDP-α-MSH binding, and the y-axis is concentration.

Fig. 2 is a graph showing erectile activity in rats with iv administration of varying quantities of 7'- amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-NH_2.

Fig. 3 is a graph of food intake in male Sprague-Dawley rats administered saline or test compounds by intracerebroventricular (ICV) dosing. Saline was given to 12 animals, Compound A (7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-Asp-Phe-NH_2) was given to 11 animals and Compound B (heptanoyl-Thr(Bzl)-D-Phe(4-Cl)-Arg-Trp-NH_2) was administered to 9 animals. At 24 hours the difference in food intake for Compound A compared to saline treatment was significant at a *p* value of < .01.

Fig. 4 is a graph of food intake in male Sprague-Dawley rats administered saline or different doses of 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-NH_2 by ICV, with the number of animals in each group shown. The difference in food intake at 24 hours for 1.0 nmol was significant at a $p < .01$, and for 0.5 nmol was significant at a $p < .05$ when compared to saline treatment. Animals receiving saline had an average daily body weight gain of 4 g, animals receiving 0.1 nmol gained 3 g, animals receiving 0.5 nmol lost 1 g and animals receiving 1.0 nmol lost 3 g. These animals returned to baseline by 48 hours after dosing.

Fig. 5 is a graph of food intake in male Sprague-Dawley rats administered saline or different doses of 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-NH_2 by intraperitoneal (IP) dosing. 12 animals were in each of the four groups (saline, 750 µg/kg, 1500 µg/kg and 3000 µg/kg). The difference in food intake for both 1500 µg/kg and 3000 µg/kg at 24 hours was significant at a *p* value of < .01. Animals receiving saline had an average daily body weight gain of 4 g, animals receiving 750 µg/kg gained 4 g, animals receiving 1500 µg/kg gained 2 g and animals receiving 3000 µg/kg lost 1 g.

Fig. 6 is a graph illustrating no conditioned taste aversion response to 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-NH_2, thereby demonstrating that observed weight lost is not due to induced illness or similar side effects. Both pre-dosing and post-dosing consumption of water with saccharin added was measured, with dosing consisting of IP administration of saline (negative control), LiCl (positive control) and the test article, 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-NH_2, administered at 1500 µg/kg.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

(BEST MODES FOR CARRYING OUT THE INVENTION)

Definitions. Certain terms as used throughout the specification and claims are defined as follows:

The terms "bind," "binding," "complex," and "complexing," as used throughout the specification and claims, are generally intended to cover all types of physical and chemical binding, reactions, complexing, attraction, chelating and the like.

The "peptides" of this invention can be a) naturally-occurring, b) produced by chemical synthesis, c) produced by recombinant DNA technology, d) produced by biochemical or enzymatic fragmentation of larger molecules, e) produced by methods resulting from a combination of methods a through d listed above, or f) produced by any other means for producing peptides.

By employing chemical synthesis, a preferred means of production, it is possible to introduce various amino acids which do not naturally occur along the chain, modify the N- or C-terminus, and the like, thereby providing for improved stability and formulation, resistance to protease degradation, and the like.

The term "peptide" as used throughout the specification and claims is intended to include any structure comprised of two or more amino acids, including chemical modifications and derivatives of amino acids. For the most part, the peptides of this invention comprise fewer than 100 amino acids, and preferably fewer than 60 amino acids, and most preferably ranging from about 2 to 20 amino acids. The amino acids forming all or a part of a peptide may be naturally occurring amino acids, stereoisomers and modifications of such amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically modified amino acids, constructs or structures designed to mimic amino acids, and the like, so that the term "peptide" includes pseudopeptides and peptidomimetics, including structures which have a non-peptidic backbone. The term "peptide" also includes dimers or multimers of peptides. A "manufactured" peptide includes a peptide produced by chemical synthesis, recombinant DNA technology, biochemical or enzymatic fragmentation of larger molecules, combinations of the foregoing or, in general, made by any other method.

The "amino acids" used in this invention, and the term as used in the specification and claims, include the known naturally occurring protein amino acids, which are referred to by both their common three letter abbreviation and single letter abbreviation. *See generally* Synthetic Peptides: A User's

Guide, GA Grant, editor, W.H. Freeman & Co., New York (1992), the teachings of which are incorporated herein by reference, including the text and table set forth at pages 11 through 24. As set forth above, the term "amino acid" also includes stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs or structures designed to mimic amino acids, and the like. Modified and unusual amino acids are described generally in Synthetic Peptides: A User's Guide, cited above; Hruby VJ, Al-obeidi F and Kazmierski W: *Biochem J* 268:249-262, 1990; and Toniolo C: *Int J Peptide Protein Res* 35:287-300, 1990; the teachings of all of which are incorporated herein by reference. In addition, the following abbreviations have the meanings giving:

Abu	-	gamma-amino butyric acid
2-Abz	-	2-amino benzoic acid
3-Abz	-	3-amino benzoic acid
4-Abz	-	4-amino benzoic acid
Achc	-	1-amino-cyclohexane-1-carboxylic acid
Acpc	-	1-amino-cyclopropane-1-carboxylic acid
12-Ado	-	12-amino dodecanoic acid
7-Ahept	-	7-amino heptanoic acid
Aib	-	alpha-aminoisobutyric acid
Aic	-	2-aminoindane-2-carboxylic acid
6-Ahx	-	6-amino hexanoic acid
Amb	-	4-(aminomethyl)-benzoic acid
Amc	-	4-(aminomethyl)-cyclohexane carboxylic acid
7'-amino-heptanoyl	-	NH_2-$(CH_2)_6CO$-
8-Aoc	-	8-amino octanoic acid
Arg(Tos)	-	N^G-para-tosyl-arginine
Asp(anilino)	-	beta-anilino-aspartic acid
Asp(3-Cl-anilino)	-	beta-(3-chloro-anilino)-aspartic acid
Asp(3,5-diCl-anilino)	-	beta-(3,5-dichloro anilino)-aspartic acid
Atc	-	2-aminotetralin-2-carboxylic acid
11-Aun	-	11-amino undecanoic acid

AVA	-	5-amino valeric acid
Bip	-	biphenylalanine
Bzl	-	benzyl
Bz	-	benzoyl
Cha	-	cyclohexylalanine
Chg	-	cyclohexylglycine
Cmpi	-	4-caboxymethyl-piperazine
Dip	-	3,3-diphenylalanine
Disc	-	1,3-dihydro-2H-isoindolecarboxylic acid
Dpr(beta-Ala)	-	N^{beta}-(3-aminopropionyl)-alpha,beta-diaminopropionic acid
Et-	-	ethyl
GAA	-	epsilon-guanidino acetic acid
GBzA	-	4-guanidino benzoic acid
B-Gpa	-	3-guanidino propionic acid
GVA(Cl)	-	beta-chloro-epsilon-guanidino valeric acid
heptanoyl	-	CH_3-$(CH_2)_5CO$-
Hphe	-	homophenylalanine
HyP	-	hydroxy proline
Idc	-	indoline-2-carboxylic acid
Igl	-	indanylglycine
Inp	-	isonipecotic acid
Lys(Z)	-	N-epsilon-benzyloxycarbonyl-lysine
Me-	-	methyl
Nal 1	-	3-(1-naphthyl)alanine
Nal 2	-	3-(2-naphthyl)alanine
(N-Bzl)Nal 2	-	N-benzyl-3-(2-naphthyl) alanine
2-Naphthylacetyl	-	2-naphthyl-CH_2CO-
(Nlys)Gly	-	N-(4-aminobutyl)-glycine
(N-PhEt)Nal 2	-	N(2-phenylethyl)-3-(2-naphthyl) alanine
OcHx	-	cyclohexyl ester

Phg	-	phenylglycine
pF-Phe	-	para-fluoro-phenylalanine
Phe(4-Br)	-	4-bromo-phenylalanine
Phe(4-CF_3)	-	4-trifluoromethyl-phenylalanine
Phe(4-Cl)	-	4-chloro-phenylalanine
Phe(2-Cl)	-	2 chloro-phenylalanine
Phe(2, 4-diCl)	-	2,4,-dichloro-phenylalanine
Phe(3,4-diCl)	-	3,4,-dichloro-phenylalanine
Phe(3,4-diF)	-	3,4,-difluoro-phenylalanine
Phe(4-I)	-	4-iodo-phenylalanine
Phe(3,4-di-OMe)	-	3,4,-dimethoxy-phenylalanine
Phe(4-Me)	-	4-methyl-phenylalanine
Phe(4-NO_2)	-	4-nitro-phenylalanine
Pip	-	pipecolic acid
3-Pya	-	3-pyridylalanine
Qal(2')	-	beta-(2-quinolyl)-alanine
Sal	-	3-styrylalanine
Sar	-	sarcosine
Ser(Bzl)	-	O-benzyl-serine
TFA	-	trifluoroacetyl
Tic	-	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
Tiq	-	1,2,3,4-tetrahydroisoquinoline-1-carboxytic acid
Tle	-	tert-butylalanine
Tpi	-	1,2,3,4-tetrahydronorharman-3-carboxylic acid
Tyr(Bzl)	-	O-benzyl-tyrosine
Tyr(BzlDiCl 2,6)	-	O-(2,6 dichloro)benzyl-tyrosine
Z	-	benzyloxycarbonyl

In the listing of compounds according to the present invention, conventional amino acid residues have their conventional meaning as given in Chapter 2400 of the Manual of Patent Examining Procedure, 7th Ed. Thus, "Nle" is norleucine; "Asp" is aspartic acid; "His" is histidine; "D-

Phe" is D-phenylalanine; "Arg" is arginine; "Trp" is tryptophan; "Lys" is lysine; "Gly" is glycine; "Pro" is proline; "Tyr" is tyrosine, "Ser" is serine and so on.

A single amino acid, including stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs or structures designed to mimic amino acids, and the like, including all of the foregoing, is sometimes referred to herein as a "residue."

The peptides disclosed herein can be used for both medical applications and animal husbandry or veterinary applications. Typically, the product is used in humans, but may also be used in other mammals. The term "patient" is intended to denote a mammalian individual, and is so used throughout the specification and in the claims. The primary applications of this invention involve human patients, but this invention may be applied to laboratory, farm, zoo, wildlife, pet, sport or other animals.

In general, the peptides of this invention may be synthesized by solid-phase synthesis and purified according to methods known in the art. Any of a number of well-known procedures utilizing a variety of resins and reagents may be used to prepare the compounds of this invention.

The peptides of this invention may be in the form of any pharmaceutically acceptable salt. Acid addition salts of the compounds of this invention are prepared in a suitable solvent from the peptide and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. The acetate salt form is especially useful. Where the compounds of this invention include an acidic moiety, suitable pharmaceutically acceptable salts may include alkali metal salts, such as sodium or potassium salts, or alkaline earth metal salts, such as calcium or magnesium salts.

The invention provides a pharmaceutical composition that includes a peptide of this invention and a pharmaceutically acceptable carrier. The carrier may be a liquid formulation, and is preferably a buffered, isotonic, aqueous solution. Pharmaceutically acceptable carriers also include excipients, such as diluents, carriers and the like, and additives, such as stabilizing agents, preservatives, solubilizing agents, buffers and the like, as hereafter described.

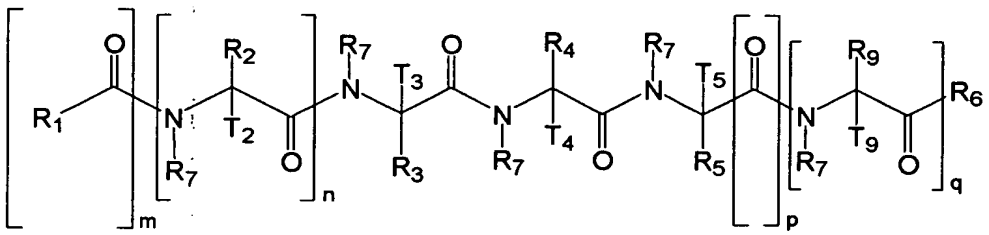
Routes of Administration. If it is administered by injection, the injection may be intravenous, subcutaneous, intramuscular, intraperitoneal or other means known in the art. The peptides of this invention may be formulated by any means known in the art, including but not limited to formulation as tablets, capsules, caplets, suspensions, powders, lyophilized preparations, suppositories, ocular

drops, skin patches, oral soluble formulations, sprays, aerosols and the like, and may be mixed and formulated with buffers, binders, excipients, stabilizers, anti-oxidants and other agents known in the art. In general, any route of administration by which the peptides of invention are introduced across an epidermal layer of cells may be employed. Administration means may include administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, nasal administration and the like. The dosage for treatment is administration, by any of the foregoing means or any other means known in the art, of an amount sufficient to bring about the desired therapeutic effect.

The peptides of this invention may be formulated or compounded into pharmaceutical compositions that include at least one peptide of this invention together with one or more pharmaceutically acceptable carriers, including excipients, such as diluents, carriers and the like, and additives, such as stabilizing agents, preservatives, solubilizing agents, buffers and the like, as may be desired. Formulation excipients may include polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate. For injection or other liquid administration formulations, water containing at least one or more buffering constituents is preferred, and stabilizing agents, preservatives and solubilizing agents may also be employed. For solid administration formulations, any of a variety of thickening, filler, bulking and carrier additives may be employed, such as starches, sugars, fatty acids and the like. For topical administration formulations, any of a variety of creams, ointments, gels, lotions and the like may be employed. For most pharmaceutical formulations, non-active ingredients will constitute the greater part, by weight or volume, of the preparation. For pharmaceutical formulations, it is also contemplated that any of a variety of measured-release, slow-release or time-release formulations and additives may be employed, so that the dosage may be formulated so as to effect delivery of a peptide of this invention over a period of time.

In general, the actual quantity of peptides of this invention administered to a patient will vary between fairly wide ranges depending upon the mode of administration, the formulation used, and the response desired.

Structure of Peptides of the Invention. This invention provides linear peptides of the following general formula:



where:

R_1 is an aliphatic L- or D-amino acid, N-acylated L- or D-aliphatic amino acid or R_8;

R_8 is, in each instance, independently selected from the group consisting of linear or branched (C_1 to C_{17}) alkyl, aryl, heteroaryl, alkene, alkenyl, or aralkyl chains selected from the following:

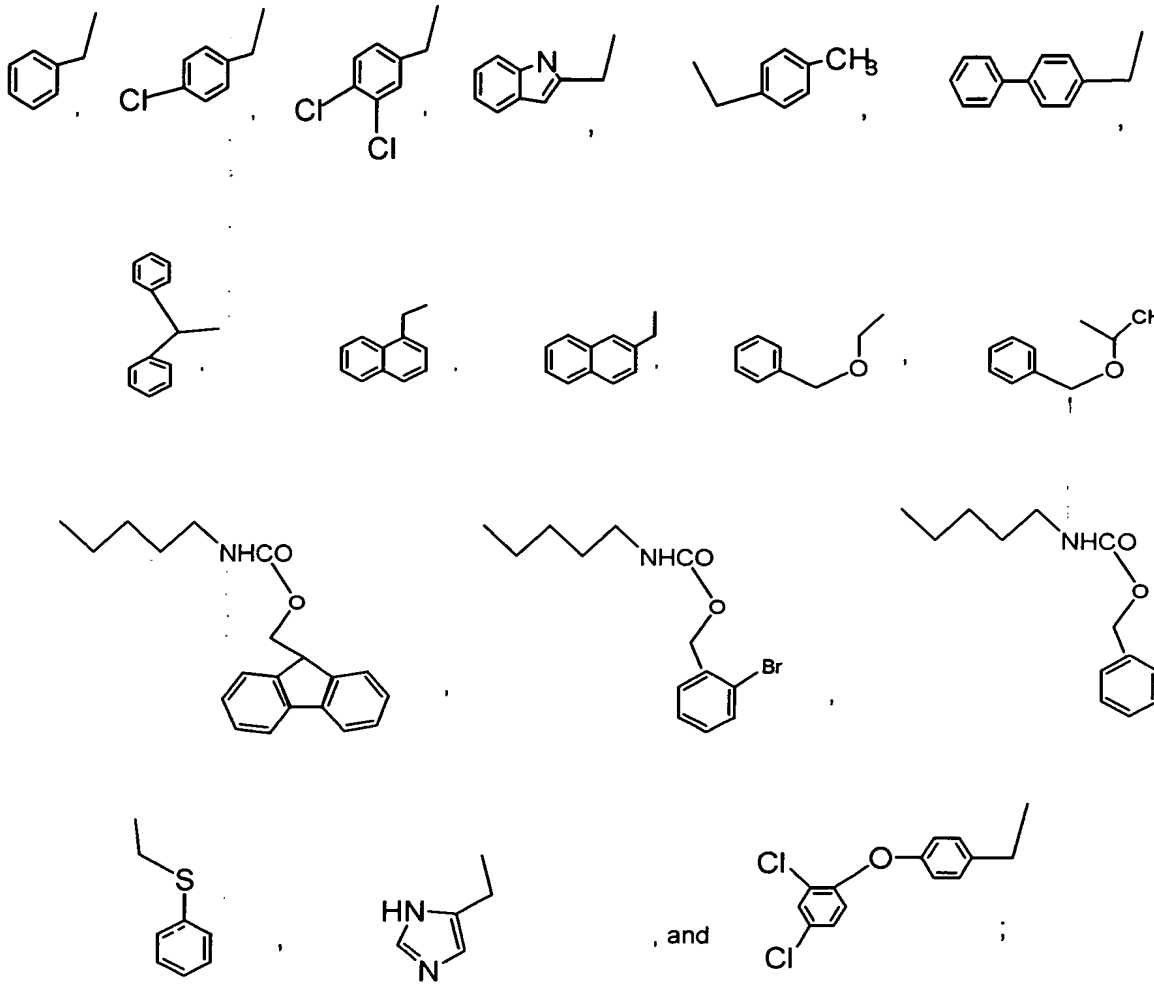
C_1 to C_{17} aliphatic linear chain or branched chain groups;

Acylated groups derived from C_1 to C_{17} linear chain or branched chain aliphatics;

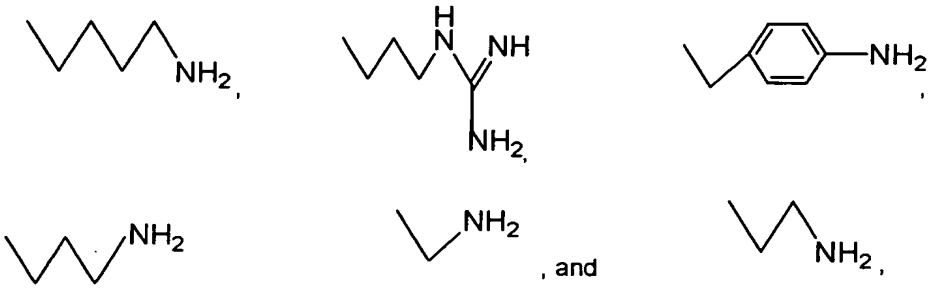
Omega amino and carboxylic derivatives of C_1 to C_{17} aliphatic linear chain or branched chain groups; and

Omega amino derivatives for acylated groups derived from C_1 to C_{17} aliphatic linear chain or branched chained aliphatics.

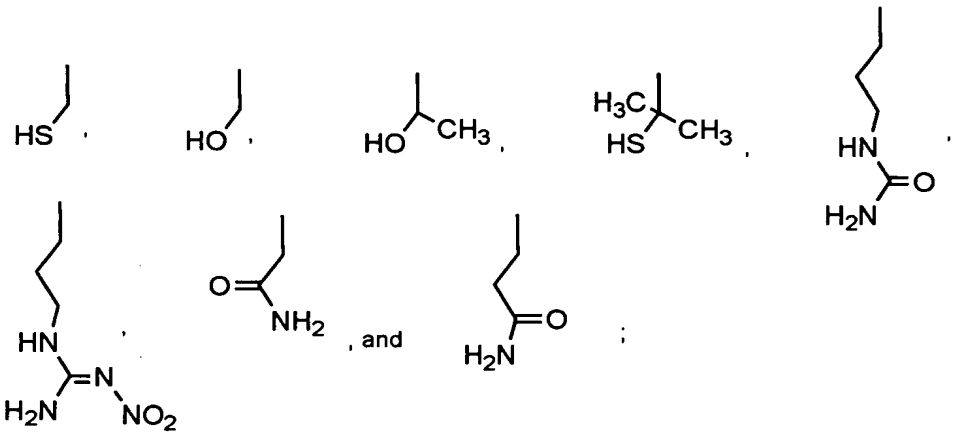
R_2 and R_3 are each H, CH_3, an aromatic substituent aryl or heteroaryl side chain of a natural or synthetic L- or D-amino acid containing at least one aromatic moiety, wherein the ring(s) may additionally be functionalized by halogen, alkyl or aryl groups, and wherein the aromatic side group is preferably selected from the following side groups:



R_4 is a positively charged aliphatic or aromatic side chain for a natural or synthetic amino acid, wherein the chain comprises at least one nitrogen-containing group, including amides, imides, amines, and nitriles, and wherein the side chain is preferably selected from the following side groups:



or is a neutral aliphatic side chain having hydrogen donors and/or acceptors, including but not limited to the following:



R_5 is H, CH_3, an aromatic substituent aryl or heteroaryl side chain of a natural or synthetic L- or D-amino acid containing at least one aromatic moiety, wherein the ring(s) may additionally be functionalized by halogen, alkyl or aryl groups, and wherein the aromatic side group is preferably selected from the side groups defined for R_2 and R_3, or a substituent alkyl or hydrogen bonding polar side chain of natural or synthetic L- or D-amino acids, wherein the side chain has a hydrogen donor or acceptor moiety;

R_6 is hydroxide, NH_2, or NH-R_8, where R_8 is preferably a short aliphatic C_1 - C_{17} chain, including an alkyl, aryl, heteroaryl, alkene, alkenyl or aralkyl;

R_7 is H, methyl, ethyl, propyl, butyl, or a similar higher linear or branched chain homolog, or a similar chain terminating in an amino group, benzyl, or similar aralkyl group;

R_9 is an amino acid side chain group, preferably selected from H, methyl, ethyl, propyl, butyl, or a similar higher linear or branched chain homolog, or a similar chain terminating in an amino group, benzyl, or similar aralkyl group;

m is normally 1 with the proviso that m may be 0 in which case this functionality is not present and the N-terminal group is an amine; and

n is normally 1 with the proviso that n may be 0 in which case this amino acid is not present;

p is normally 1 with the proviso that when p is 0 the chain terminates with the combination of R_5 and T_5 and there is no q and no R_6; and

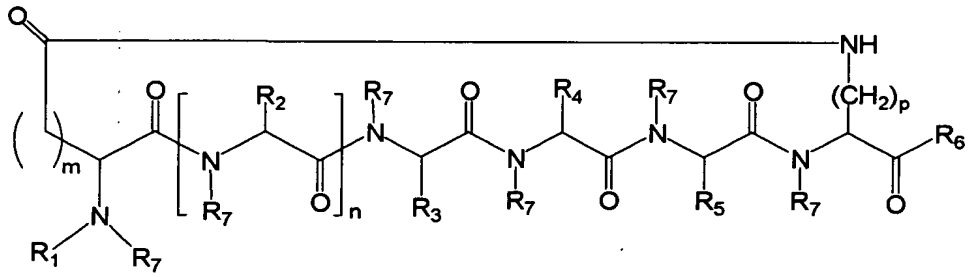
q is normally 1 with the proviso that when q is 0 and p is 1 then the terminal group is R_6; and

T_2, T_3, T_4, T_5, and T_9 are each H, CH_3, C_2H_5 or a benzyl group;

provided that one or more of the pairs R_2 and T_2, or R_3 and T_3, or R_4 and T_4, or R_5 and T_5, or R_9 and T_9 moieties may be joined together by additional carbon-carbon bonds to form a ring structure, and preferably a five-, six- or seven-membered ring structure; and

further provided that one or more of R_2, R_4, R_5 or R_9 may be joined to the R_7 group that immediately precedes such R_2, R_4, R_5 or R_9 group by additional carbon-carbon bonds to form a ring structure, and preferably a five-, six- or seven-membered ring structure, thereby fixing such R_2, R_4, R_5 or R_9 group to the immediately preceding nitrogen atom.

In another embodiment, the invention provides cyclic peptides of the following general formula:



where:

R_1 is H, an aliphatic L- or D-amino acid, N-acylated L- or D-aliphatic amino acid or R_8;

R_8 is, in each instance, independently selected from the group consisting of linear or branched (C_1 to C_{17}) alkyl, aryl, heteroaryl, alkene, alkenyl, or aralkyl chains selected from the following:

C_1 to C_{17} aliphatic linear chain or branched chain groups;

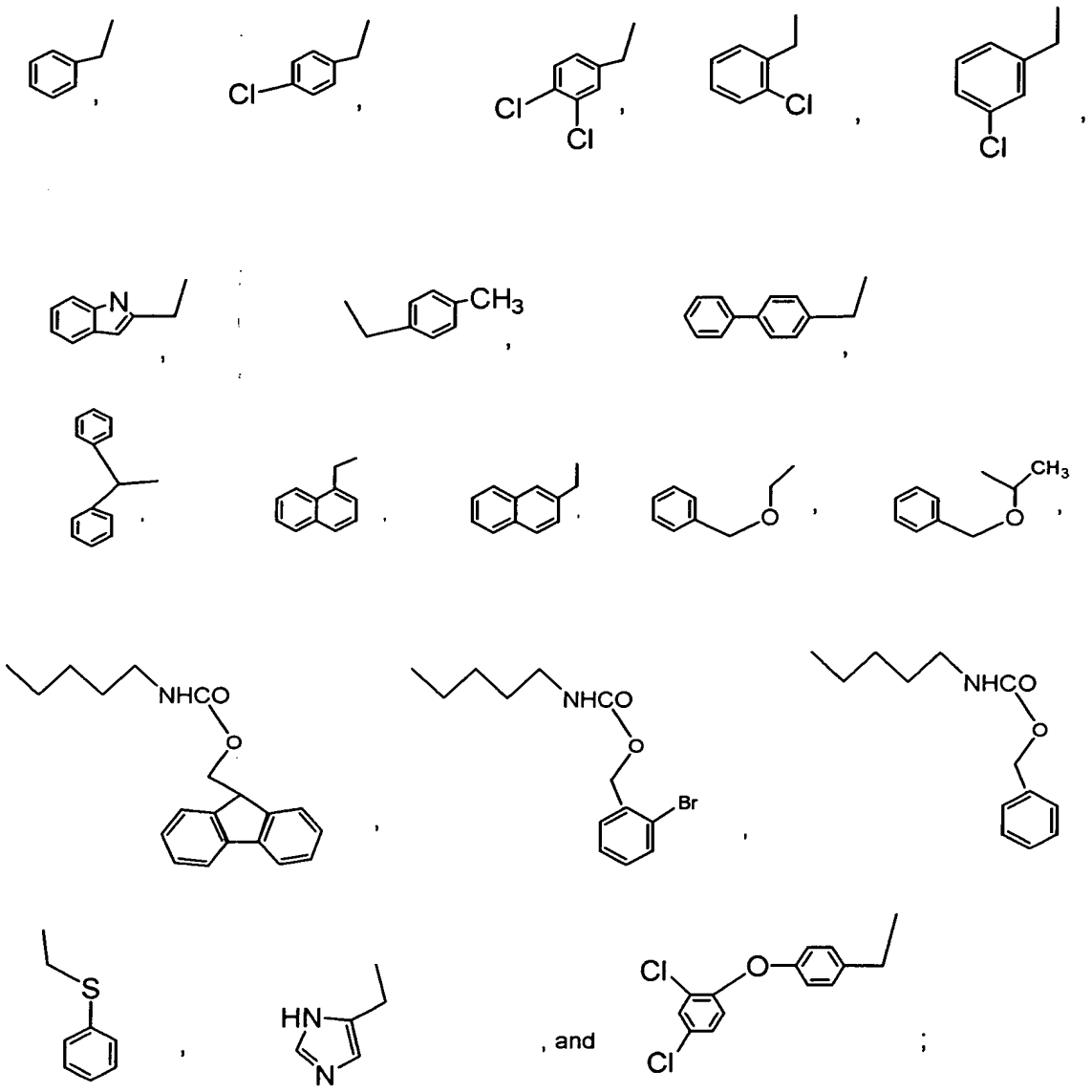
Acylated groups derived from C_1 to C_{17} linear chain or branched chain aliphatics;

Omega amino derivatives of C_1 to C_{17} aliphatic linear chain or branched chain groups; and

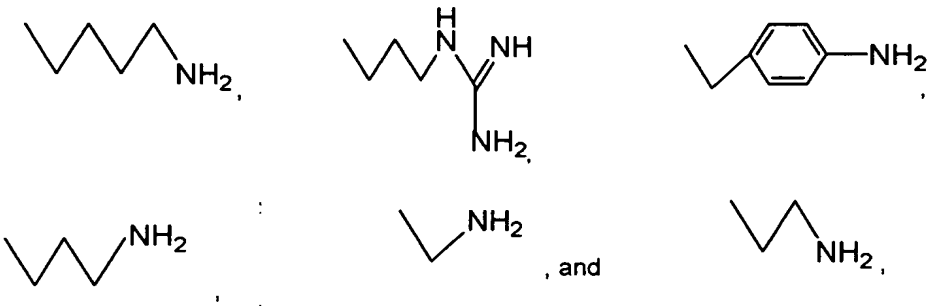
Omega amino derivatives for acylated groups derived from C_1 to C_{17} aliphatic linear chain or branched chain aliphatics.

R_2, R_3 and R_5 are each H, CH_3, an aromatic substituent aryl or heteroaryl side chain of a natural or synthetic L- or D-amino acid containing at least one aromatic moiety, wherein the ring(s)

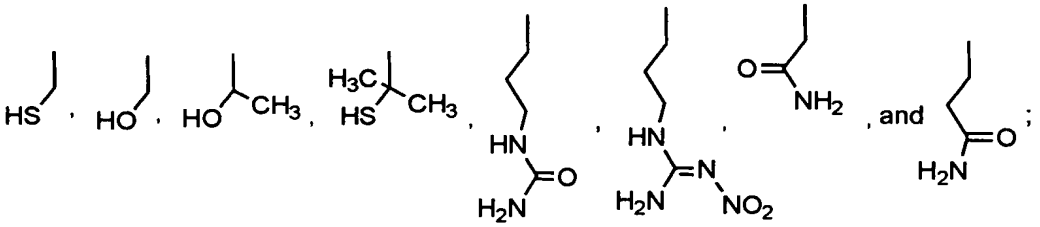
may additionally be functionalized by halogen, alkyl or aryl groups, and wherein the aromatic side group is preferably selected from the following side groups:



R_4 is a positively charged aliphatic or aromatic side chain of a natural or synthetic L- or D-amino acid, wherein the chain comprises at least one nitrogen-containing group, including amides, imides, amines, and nitriles, and wherein the side group is preferably selected from the following side groups:



or is a neutral aliphatic side chain having hydrogen donors and/or acceptors, including but not limited to the following:



R_6 is hydroxide, NH_2, or NH-R_8, where R_8 is preferably a short aliphatic C_1 - C_{17} chain, including an alkyl, aryl, heteroaryl, alkene, alkenyl, or aralkyl;

R_7 is H, methyl, ethyl, propyl, butyl, or a similar higher linear or branched chain homolog, or a similar chain terminating in an amino group, benzyl, or similar aralkyl group;

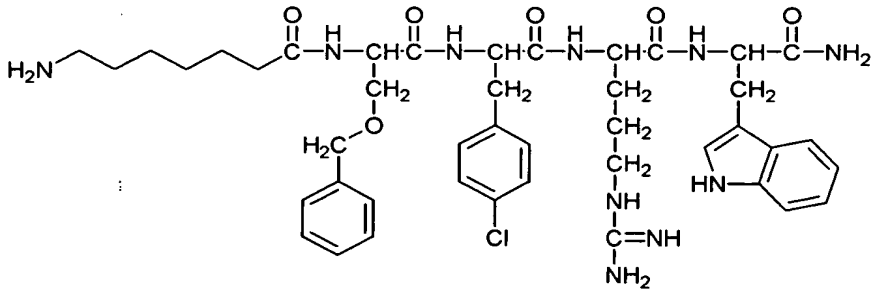
m is 1 or 2;

n is normally 1 with the proviso that n may be 0 in which case this amino acid is not present; and

p is 1 to 5.

Peptides of the Invention. Peptides of this invention were made using art conventional synthesis methods, and selected peptides were tested using a binding assay. **Tables 1** and **2** set forth linear peptides of this invention and the results of competitive inhibition binding assays, while **Tables 3** and **4** set forth cyclic peptides of this invention and the results of competitive inhibition binding assays.

In a preferred embodiment, the invention provides the peptide of the invention of the sequence 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-NH_2 having the following structure:



Competitive inhibition binding assays were conducted on peptides of the invention using membranes prepared from hMC3-R, hMC4-R, hMC5-R, and B-16 mouse melanoma cells (containing MC1-R) using 0.4 nM ^{125}I-NDP-alpha-MSH (New England Nuclear, Boston, MA, USA) in 50 mM HEPES buffer containing 1 mM $MgCl_2$, 2 mM $CaCl_2$, and 5 mM KCl, at pH 7.2. The assay tube also contained a chosen concentration of the test peptide of this invention, complexed to a rhenium metal ion as indicated, for determining its efficacy in inhibiting the binding of ^{125}I-NDP-alpha-MSH to its receptor. Non-specific binding was measured by complete inhibition of binding of ^{125}I-NDP-alpha-MSH in the assay with the presence of 1 μM alpha-MSH. Incubation was for 90 minutes at room temperature, after which the assay mixture was filtered and the membranes washed three times with ice cold buffer. The filter was dried and counted in a gamma counter for remaining radioactivity bound to the membranes. 100% specific binding was defined as the difference in radioactivity (cpm) bound to cell membranes in the absence and presence of 1 μM alpha-MSH. The cpm obtained in presence of test compounds were normalized with respect to 100% specific binding to determine the percent inhibition of ^{125}I-NDP-alpha MSH binding. Each assay was conducted in triplicate and the actual mean values, as percent inhibition, are provided in **Tables 1, 2, 3** and **4**.

Table 1 - Linear Peptides

S_1	S_2	S_3	S_4	S_5	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-Cys-NH_2	27	76	97	99
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	60	98	97	97
7'-amino-heptanoyl-	D-Ala	D-Phe(4-Cl)-	Arg-	Trp-NH_2	30	0	31	1
2'-naphthylacetyl-	Val-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	65	56	92	69
2'-naphthylacetyl-	Leu-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	81	75	96	74
2'-naphthylacetyl-	Chg-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	73	57	93	78
2'-naphthylacetyl-	Aib-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	16	39	86	52
2'-naphthylacetyl	-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	34	0	60	58
2'-naphthylacetyl-	Tle-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	67	35	93	66
1-amino-1-cyclohexanecarbonyl	-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	51	30	62	31
2'-naphthylacetyl-	1-amino-1-cyclohexanecarbonyl-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	25	35	92	63
2'-naphthylacetyl-	Ala-	D-Nal 2-	Arg-	Trp-NH_2	28	88	97	77
2'-naphthylacetyl-	D-Ala-	D-Nal 2-	Arg-	Trp-NH_2	1	34	77	44
2'-naphthylacetyl-	beta-Ala-	D-Nal 2-	Arg-	Trp-NH_2	1	58	89	59
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	D-Trp-NH_2	76	83	98	86
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-Val-NH_2	56	78	98	92
heptanoyl-	Ser(Bzl)-	Arg-	D-Phe(4-Cl)-	Trp-NH_2	77	0	18	26
heptanoyl-	Ser(Bzl)-	D-Phe-	Arg-	Trp-NH_2	75	52	88	38
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	D-Trp-NH_2	61	79	97	46
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe-	Arg-	Trp-NH_2	63	37	89	6

Table 1 - Linear Peptides

S_1	S_2	S_3	S_4	S_5	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
2'-naphthylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	D-Trp-NH_2	75	79	92	40
2'-naphthylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	45	66	91	25
3'-chlorophenylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	92	97	98	71
2'-naphthylacetyl-	Sar-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	47	65	87	44
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	(Nlys)Gly-	Trp-NH_2	49	0	15	25
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	33	94	99	73
heptanoyl-	Ser(Bzl)-	D-Nal 2-	Arg-	Trp-NH_2	3	89	98	97
7'-amino-heptanoyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	58	75	88	15
7'-amino-heptanoyl-	beta-Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	25	0	22	2
Ph-$(CH_2)_2$NH-	$CO(CH_2)_2CO$-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	67	82	90	54
4'-bromophenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	29	97	95	65
3',4'-dichlorophenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	40	100	98	81
2',4'-dichlorophenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	0	85	92	38
4'-biphenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	0	54	88	37
2'-naphthoyl-	Inp-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	10	19	59	19
2'-naphthylacetyl-	Inp-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	2	15	58	36
4'-phenylbutylamino-carbonyl	-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	0	0	45	49
3'-phenylpropylamino-carbonyl	-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	0	3	60	51
4'phenylbutyryl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	20	79	94	46
2'-naphthoyl-	Pip-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	5	12	46	32
2'-naphthylacetyl-	Pip-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	12	54	77	55

Table 1 - Linear Peptides

S_1	S_2	S_3	S_4	S_5	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Lys-	Trp-NH_2	0	35	85	48
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Phe-NH_2	0	31	63	32
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	3'-Pya-NH_2	0	0	24	19
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Trp-	4'-amino-butylamide	0	0	17	30
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	MeTrp-NH_2	71	92	99	85
heptanoyl-	MeThr(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	4	18	78	39
heptanoyl-	Thr(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	28	39	91	65
heptanoyl-	D-Thr(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	11	4	19	31
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	beta-Ala-Trp-NH_2	20	13	25	44
2'-bromophenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	40	81	93	36
3'-bromophenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	86	97	98	90
4'-CF_3phenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	70	98	98	69
3'-CF_3phenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	96	101	100	96
2'-CF_3phenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	41	85	92	35
3',5'-CF_3phenylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	89	95	98	92
2',5'-CF_3phenylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	75	79	95	75
4'-Mephenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	56	93	96	61
3'-Mephenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	77	94	96	74
2'-Mephenyl-acetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	44	86	93	50
heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Dpr(beta-Ala)-	Trp-NH_2	5	21	65	28
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-OH	35	34	67	25
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	MeTrp-NH_2	76	95	99	86
beta-Ala-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	66	89	99	86

Table 1 - Linear Peptides

S_1	S_2	S_3	S_4	S_5	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
4-aminoButyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	63	90	99	78
5-aminoValeryl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	57	88	98	71
6-aminoCaproyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	69	91	99	75
aminoTranexamyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	56	90	98	74
Cmpi-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	66	88	99	79
7'-amino-heptanoyl-	Thr(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	38	48	94	68
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	D-Nal 1-NH_2	25	24	71	36
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Nal 1-NH_2	21	60	95	49
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	D-Tic-NH_2	3	0	6	10
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Tic-NH_2	45	0	19	20
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	D-Nal 2-NH_2	50	93	99	78
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Nal 2-NH_2	64	95	100	90
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	D-Arg-	Trp-NH_2	18	1	12	27
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	1-aminoindane-1-caboxyl-NH_2	21	0	8	12
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Aic-NH_2	3	0	33	13
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Atc-NH_2	7	34	84	27
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Tpi-NH_2	18	50	80	37
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	D-Tpi-NH_2	16	7	51	29
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Tiq-NH_2	8	0	8	24
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	D-Tiq-NH_2	8	0	2	23
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Lys-	Trp-NH_2	22	51	83	33
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	homoLys-	Trp-NH_2	27	33	71	8
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	alpha-(N-amidino-4'-piperidine) Gly	Trp-NH_2	3	8	26	16
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	(4'-guanidino)	Trp-NH_2	3	8	22	27

Table 1 - Linear Peptides

S_1	S_2	S_3	S_4	S_5	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
			Gly					
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	D-(4-guanidino) Phe	Trp-NH_2	0	9	0	8
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	beta-(N-amidino-4'-peperidine) Ala	Trp-NH_2	0	13	56	8
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Tryptamide	36	74	97	54
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	NMe-Tryptamide	56	55	96	66
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	alpha-Me-Tryptamide	61	84	99	71
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	2'-(4"-methylphenyl)ethyl amide	38	67	90	43
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	3',4'-Cl_2phenylmethylamide	8	32	41	28
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	1'-aminoindan	28	26	57	0
3',4'-Cl_2phenylacetyl-	Ala-	D-Phe-	Arg-	Trp-NH_2	75	80	83	38
3',4'-Cl_2phenylacetyl-	Ala-	D-Phe(3,4-F_2)-	Arg-	Trp-NH_2	72	92	93	51
3',4'-Cl_2phenylacetyl-	Ala-	D-Val-	Arg-	Trp-NH_2	0	0	2	0
3',4'-Cl_2phenylacetyl-	Ala-	D-Phe(4-Cl)-	Lys-	Trp-NH_2	45	84	85	52
3',4'-Cl_2phenylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	3'-phenylpropylamide	0	44	39	16
3',4'-Cl_2phenylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	2'-(4"-methylphenyl)ethyl amide	33	77	79	-6
3'-CF_3phenylacetyl-	Ala-	D-Phe-	Arg-	Trp-NH_2	85	55	72	41
3'-CF_3phenylacetyl-	Ala-	D-Phe(3,4-F_2)-	Arg-	Trp-NH_2	87	77	90	71
3'-CF_3phenylacetyl-	Ala-	D-Val-	Arg-	Trp-NH_2	2	0	0	1

Table 1 - Linear Peptides

S_1	S_2	S_3	S_4	S_5	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
3'-CF_3phenylacetyl-	Ala-	D-Phe(4-Cl)-	Lys-	Trp-NH_2	75	64	84	67
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Disc-NH_2	0	0	0	18
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	3'-phenylpropylamide	14	12	30	34
3'-CF_3phenylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Tryptamide	87	94	98	89
3'-CF_3phenylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	2'-(4"-methylphenyl)ethyl amide	59	64	75	27
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	2',4'-dichlorobenzylamide	9	5	20	-6
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)	Arg-	3'-(1H-imidazol)propylamide	2	7	4	16
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)	Arg-	4-phenyl-piperidine-4-carbonamide	5	2	13	25
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)	Arg-	3-phenyl-1-propylamide	11	23	49	28
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	2,4-dichlorophenethylamide	19	43	86	54
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	homo-Ala-4-pip(N-amidino)-	Trp-NH_2	4	8	34	17
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	S-(-)-1-(2-Naphthyl)ethylamide	3	1	59	33
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	S-(-)-1-(1-Naphthyl)ethylamide	46	85	98	64
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	2'-	10	15	34	44

Table 1 - Linear Peptides								
S_1	S_2	S_3	S_4	S_5	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
				methylbenzylamide				
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	3'-methylbenzylamide	18	11	35	38
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	4'-methylbenzylamide	7	22	42	44
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	2',2'-diphenylethylamide	4	11	24	34
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	4'-(2"-pyridyl)piperazineamide	12	7	30	30
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	N-benzylmethylamide	17	12	34	33
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	1',2'-diphenylethylamide	14	42	92	52
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Histamide	4	0	9	-2
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	R-(+)-1-(2-Naphthyl)ethylamide	3	0	21	26
7'-amino-heptanoyl-	Ser(Bzl)-	D-Nal 2-	Arg-	Trp-NH_2	4	93	99	82
7'-amino-heptanoyl-	Ala-	D-Nal 2-	Arg-	Trp-NH_2	0	57	84	15
7'-amino-heptanoyl-	D-Ala-	D-Nal 2-	Arg-	Trp-NH_2	0	0	19	0
	Ser(Bzl)-	D-Nal 2-	Arg-	Trp-NH_2	10	35	92	64
	Ser(Bzl)-	D-Nal 2-	Arg-	D-Trp-NH_2	21	51	90	74
7'-amino-heptanoyl-	Ser(Bzl)-	D-Nal 2-	Arg-	D-Trp-NH_2	-8	86	100	82
2'-Naphthylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-Asp-NH_2	65	96	98	68
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-Asp-NH_2	35	73	98	48
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-Asp-Phe-NH_2	34	37	100	54
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Asp-Trp-NH_2	59	0	12	10
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Ala-Trp-NH_2	60	10	31	42
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-Ala-NH_2	60	93	100	79

Table 1 - Linear Peptides								
S_1	S_2	S_3	S_4	S_5	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	phenethylamide	25	50	75	50
7'-amino-heptanoyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-Asp-OH	4	16	67	3
7'-amino-heptanoyl-	Ser-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	19	61	69	11
7'-amino-heptanoyl-	Ser(Bzl)-	Phe(4-Cl)-	Arg-	Trp-NH_2 (SEQ ID NO:2)	4	10	0	52
	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	27	65	86	65

Table 2 - Linear Peptides									
S_1	S_2	S_3	S_4	S_5	Conc. µM	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
Ac-Nle-Asp-	His-	D-Phe-	Orn-	Trp-Lys[N-epsilon (=C(NMe_2)$_2$)]-NH_2	10	102		72	
Ac-Nle-Asp-	His-	D-Phe-	Cit-	Trp-Lys[N-epsilon (=C(NMe_2)$_2$)]-NH_2	1	87		62	
Ac-Nle-Asp-	His-	His-	Arg-	Trp-Lys-NH_2 (SEQ ID NO:3)	1	34		28	
Ac-	His-	Phe-	Cys-	Trp-NH_2 (SEQ ID NO:4)	10	54		29	
Ac-	His-	D-Phe-	Cys-	Trp-NH_2	10	91		8	
Ac-	His-	D-Phe-	Cys-	Trp-NH_2	1	65			
Ac-Nle-Ala-	His-	D-Phe-	Arg-	Cys-Trp-NH_2	1	101		57	
Ac-Nle-Ala-His-	His-	D-Phe-	Arg-	Cys-Trp-NH_2	0.1	95		43	
heptanoyl-	His-	D-Phe-	Arg-	Cys-Trp-NH_2	1	97		55	
heptanoyl-	His-	D-Phe-	Arg-	Cys-Trp-NH_2	0.1	75		36	
HOOC-(CH_2)$_5$-CO-	His-	D-Phe-	Arg-	Cys-Trp-NH_2	1	95		29	
HOOC-(CH_2)$_5$-CO-	His-	D-Phe-	Arg-	Cys-Trp-NH_2	0.1	76		1	
NH_2-(CH_2)$_5$-CO-	His-	D-Phe-	Arg-	Cys-Trp-NH_2	1	96		56	
NH_2-(CH_2)$_5$-CO-	His-	D-Phe-	Arg-	Cys-Trp-NH_2	0.1	87		7	
Ac-Nle-Asp-	His-	D-Phe-	Cit-	Trp-Lys-NH_2	1	90		92	
Ac-Nle-Asp-	His-	D-Phe-	Cit-	Trp-Lys-NH_2	0.1	55		28	
Ac-Nle-Asp-	His-	D-Phe-	Cit-	Trp-Lys-NH_2	0.01	33		24	
Ac-Nle-Asp-	His-	D-Phe-	Arg-	Trp-Lys-OH	1	90	18	53	15
Ac-Nle-Ala-	His-	D-Phe-	Arg-	Trp-NH_2	1	101	84	95	77
Ac-Nle-Ala-	His-	D-Phe-	Arg-	Trp-Cys-NH_2	1	97	58	93	100
heptanoyl-	Ser(Bzl)-	D-Nal 2-	Arg-	Trp-NH_2	1	3	89	98	97
heptanoyl-	Ser(Bzl)-	D-Nal 2-	Arg-	Trp-Cys-NH_2	1	2	72	97	101
2-Naphthylacetyl-	Ser(Bzl)-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	1	15	93	98	71
2-Naphthylacetyl-	D-Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	1	5	18	56	26
4'-chlorophenylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	1	62	90	95	68

2'-chlorophenylacetyl-	Ala-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	1	3	48	87	28
Ph-$(CH_2)_2$NH-	$CO(CH_2)_2CO$-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	1	67	82	90	54
Ph-$(CH_2)_2$NH-CO	-	D-Phe(4-Cl)-	Arg-	Trp-NH_2	1	1	11	63	27

Table 3 - Cyclic Peptides

S_1	S_2	S_3	S_4	S_5	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
Cyclo1,6 [2-Naphthylacetyl-Asp-	Ser(Bzl)-	D-Phe(2-Cl)-	Arg-	Trp-Lys-NH_2]	16	87	97	44
Cyclo1,6 [heptanoyl-Asp-	His-	D-Phe(2-Cl)-	Arg-	Trp-Lys-NH_2]	99	80	100	98
Cyclo1,6 [2-Naphthylacetyl-Asp-	His-	D-Nal 2-	Arg-	Trp-Lys-NH_2]	89	85	100	94
Cyclo1,6 [heptanoyl-Asp-	Ser(Bzl)-	D-Phe(2-Cl)-	Arg-	Trp-Lys-NH_2]	86	84	99	98

Table 4 - Cyclic Peptides

S_1	S_2	S_3	S_4	S_5	Conc. µM	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe(3,4-diCl)-	Arg-	Trp-Lys-NH_2]	1	98		103	
Cyclo1,6 [heptanoyl-Asp-	Ser(Bzl)-	D-Phe(3-Cl)-	Arg-	D-Nal 2-Lys-NH_2]	1	85		100	
Cyclo1,6 [heptanoyl-Asp-	Ser(Bzl)-	D-Phe(3-Cl)-	Arg-	D-Nal 2-Lys-NH_2]	0.1	48		97	
Cyclo1,6 [heptanoyl-Asp-	Ser(Bzl)-	D-Phe(3-Cl)-	Arg-	D-Nal 2-Lys-NH_2]	0.01	26		74	
Cyclo1,6 [heptanoyl-Asp-	Nal 2-	D-Phe(3-Cl)-	Arg-	Ser(Bzl)-Lys- NH_2]	1	51		82	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Cit-	Trp-Lys-NH_2]	1	95		100	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Cit-	Trp-Lys-NH_2]	0.1	88		95	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Cit-	Trp-Lys-NH_2]	0.01	70		72	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Orn-	Trp-Lys-NH_2]	0.1	75		60	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Orn-	Trp-Lys-NH_2]	0.01	53		17	
Cyclo2,7 [Ac-Nle-Asp-	His-	Phe-	Arg-	Trp-Lys-NH_2]	0.1	74		60	

Table 4 - Cyclic Peptides									
S_1	S_2	S_3	S_4	S_5	Conc. µM	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
Cyclo2,7 [Ac-Nle-Asp-	His-	Phe-	Arg-	Trp-Lys-NH_2]	0.01	50		24	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Ser-	Trp-Lys-NH_2]	0.1	60		20	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Ser-	Trp-Lys-NH_2]	0.01	41		21	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Lys-	Trp-Lys-NH_2]	1	100		93	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Lys-	Trp-Lys-NH_2]	0.1	98		93	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Lys-	Trp-Lys-NH_2]	0.01	88		51	
Cyclo2,7 [Ac-Nle-Asp-	His-	MePhe-	Arg-	Trp-Lys-NH_2]	1	32		22	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-MePhe	Arg-	Trp-Lys-NH_2]	0.1	1		46	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-MePhe-	Arg-	Trp-Lys-NH_2]	1	44		70	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	MeArg-	Trp-Lys-NH_2]	1	100		100	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	MeArg-	Trp-Lys-NH_2]	0.1	100		92	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	MeArg-	Trp-Lys-NH_2]	0.01	95		66	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	MeArg-	Trp-Lys-NH_2]	0.001	69		38	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	MeArg-	Trp-Lys-NH_2]	1	97		96	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Arg-	MeTrp-Lys-NH_2]	1	99		100	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Arg-	MeTrp-Lys-NH_2]	0.1	94		93	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Arg-	MeTrp-Lys-NH_2]	0.01	66		60	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe-	Arg-	MeTrp-Lys-NH_2]	0.001	35		41	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Tpi-	Arg-	Trp-Lys-NH_2]	1	53		81	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-MePhe-	Arg-	Trp-Orn-NH_2]	1	52		60	
Cyclo2,7 [Ac-Nle-Glu-	His-	D-MePhe-	Arg-	Trp-Lys-NH_2]	1	59		43	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Tic-	Arg-	Trp-Lys-NH_2]	1	28		31	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-MePhe-	Arg-	MeTrp-Lys-NH_2]	1	62		85	
Cyclo2,7 [Ac-Nle-Asp-	Arg-	D-Nal 2'-	Arg-	Trp-Lys-NH_2]	1	96	97	100	100
Cyclo2,7 [Ac-Nle-Asp-	His-	D-MePhe-	MeArg-	Trp-Lys-NH_2]	1	39		39	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe(3-Cl)-	Arg-	Trp-Lys-NH_2]	1	84	77	99	85
Cyclo1,6 [heptanoyl-Asp-	His-	D-Phe-	Arg-	Trp-Lys-OH]	1	73		97	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Phe(2-Cl)-	Arg-	Trp-Lys-NH_2]	0.1	99		100	
Cyclo2,7 [Ac-Nle-Asp-	His-	D-Tiq-	Arg-	Trp-Lys-NH_2]	1	20		15	
Cyclo1,6 [heptanoyl-Asp-	Ser(Bzl)-	D-Phe(3-Cl)-	Arg-	Trp-Lys-NH_2]	1	66	92	100	97
Cyclo1,6 [heptanoyl-Asp-	Ser(Bzl)-	D-Phe(3-Cl)-	Arg-	Trp-Lys-NH_2]	0.1	64		99	

Table 4 - Cyclic Peptides									
S_1	S_2	S_3	S_4	S_5	Conc. µM	MC1-R (B-16)	MC3-R	MC4-R	MC5-R
Cyclo1,6 [heptanoyl-Asp-	Ser(Bzl)-	D-Phe(3-Cl)-	Arg-	Trp-Lys-NH_2]	0.01	28		88	
Cyclo1,6 [heptanoyl-Asp-	Ser(Bzl)-	D-Phe(3-Cl)-	Arg-	Trp-Lys-NH_2]	0.001	13		25	
Cyclo1,6 [heptanoyl-Asp-	His-	D-Phe(3-Cl)-	Arg-	Nal 2'-Lys-NH_2]	0.01	73		82	
Cyclo1,6 [heptanoyl-Asp-	His-	D-Phe(3-Cl)-	Arg-	Nal 2'-Lys-NH_2]	0.001	42		7	
Cyclo1,6 [heptanoyl-Asp-	His-	D-Phe(3-Cl)-	Arg-	Nal 2'-Lys-NH_2]	0.0001	18		0	
Cyclo1,6 [heptanoyl-Asp-	Thr(Bzl)-	D-Phe(3-Cl)-	Arg-	Trp-Lys-NH_2]	1	59	79	99	91
Cyclo1,6 [heptanoyl-Asp-	Ser(Bzl)-	D-Phe(3-Cl)-	Arg-	D-Trp-Lys-NH_2]	1	66	90	98	99
Cyclo1,6 [2-Naphthylacetyl-Asp-	Ser(Bzl)-	D-Phe(3-Cl)-	Arg-	Trp-Lys-NH_2]	1	5	68	88	69
Cyclo1,6 [heptanoyl-Asp-	His-	D-Phe(3-Cl)-	Arg-	Trp-Lys-NH_2]	1	94	78	97	71
cyclo1,5[2-Naphthylacetyl-Asp	-	D-Phe(2-Cl)-	Arg-	Trp-Lys-NH_2]	1	19	7	67	20
cyclo1,6[2-Naphthylacetyl-Asp-	Ala-	D-Phe(2-Cl)-	Arg-	Trp-Lys-NH_2]	1	62	82	98	73
cyclo2,7[Ac-Nle-Asp-	His-	D-Me(homo) Phe-	Arg-	Trp-Lys-NH_2]	1	2	4	0	2
cyclo2,7[Ac-Nle-Asp-	His-	D-EtPhe-	Arg-	Trp-Lys-NH_2]	1	80	37	53	39
cyclo2,7[Ac-Nle-Asp-	His-	D-Phe-	MeArg-	MeTrp-Lys-NH_2]	1	94	3	53	29
cyclo2,7[Ac-Nle-Asp-	MeHis-	D-Phe-	Arg-	Trp-Lys-NH_2]	1	N.D.	N.D.	N.D.	N.D.

The invention is further illustrated by the following non-limiting examples.

EXAMPLE 1

The Ki (nM) of certain peptides were determined, as was the agonist/antagonist status with respect to MC4-R. Functional evaluation of peptides at MC4-R was performed by measuring the accumulation of intracellular cAMP in HEK-293 cells expressing MC4-R. Antagonistic activity was determined by measuring the inhibition of α-MSH -induced cAMP levels following exposure to the compounds. Cells, suspended in Earle's Balanced Salt Solution containing 10 mM HEPES, pH 7.5, 5 mM $MgCl_2$, 1 mM glutamine, 0.1% albumin and 0.6 mM 3-isobutyl-1-methyl-xanthine, a phosphodiesterase inhibitor, were plated in 96 well plates at a density of 0.5×10^5 cells per well. Cells were incubated with the test peptides in the presence or absence of α-MSH for 1 hour at 37° C. cAMP levels were measured by EIA (Amersham) in the cell lysates. Data analysis and EC_{50} values were determined using nonlinear regression analysis with Prism Graph-Pad software.

Table 5

	Ki (nM)				
	MC-1 B-16	MC-3 Mem	MC-4 Mem	MC-5 Mem	HEK-293 (MC4-R) cells Classification
7'-amino-heptanoyl-Ser(Bzl)-D-Nal 2-Arg-Trp-NH_2	1865	50	4	102	Antagonist
7'-amino-heptanoyl-Ser(Bzl)-D-Nal 2-Arg-D-Trp-NH_2	1296	70	6	90	Antagonist
7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-Asp-NH_2	760	191	9	596	Agonist
7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-Asp-Phe-NH_2	269	318	12	386	Agonist
7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-Ala-NH_2	142	37	2	112	Agonist
7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4-Cl)-Arg-Trp-NH_2	795	25	1	175	Agonist

Fig. 1 is a graph of displacement of I^{125}-NDP-α-MSH bound to MC1-R, MC3-R, MC4-R and MC5-R using varying concentrations of 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4'-Cl)-Arg-Trp-NH_2, showing the binding affinity curves.

EXAMPLE 2

The ability of compounds to induce penile erection (PE) in male rats was evaluated with selected peptides. Male Sprague-Dawley rats weighing 200-250 g were kept on a 12 hour on/off light

cycle with food and water *ad libitum*. All behavioral studies were performed between 10 a.m. and 5 p.m. Groups of 4-8 rats were treated with peptides at a variety of doses via intravenous (IV), subcutaneous (SC), intracerebroventricular (ICV), intraperitoneal (IP) injection or administered intranasally (IN) using a micropipetor to deliver 25 µL of solution into one nostril. Immediately after treatment, rats were placed into individual polystyrene cages (27 cm long, 16 cm wide, and 25 cm high) for behavioral observation. Rats were observed for 30 minutes and the number of yawns, grooming bouts and PEs were recorded in three 10-minute bins. As shown in Fig. 2, selected peptides, including 7'- amino-heptanoyl-Ser(Bzl)-D-Phe(4'-Cl)-Arg-Trp-NH_2, induced erections in male rats.

EXAMPLE 3

Food intake and body weight change was evaluated for selected peptides. Male Sprague-Dawley rats weighing ~300 g at the beginning of the experiment were kept on a 12 hour on/of light cycle. Lights out was adjusted to 12:00 p.m. to allow for dosing just prior to the start of their dark period. Rats (12/group) were fed powdered chow and water *ad libitum*. For 1 week before treatment, 24-hour food intake and body weight change was recorded to assess a baseline for the group during vehicle treatment. The rats were dosed ICV, IV, SC or IP on day 0 and food intake and body weight measured daily for 1 week. Animals were dosed once per week for up to 6 weeks and their food intake and daily weight changed compared to their baseline. Figs. 3, 4 and 5 illustrate results of different peptides at different doses and by varying routes of administration.

EXAMPLE 4

Conditioned taste aversion was evaluated in rats using selected peptides. Male Sprague-Dawley rats weighing ~300 g were kept on a 12 hour on/of light cycle. Lights out was adjusted to 12:00 p.m. with food *ad libitum*. Animals were trained to be accustomed to 30 minutes of access to water per day. On day 1 of the experiment, rats were given 30 minutes of access to water containing 0.15% saccharin immediately prior to being dosed ICV, IV or IP with compound. On day 2 they were given plain water for the appointed time. On day 3 the rats were given saccharin-containing water again. The amount of fluid these animals consumed on day 1 and day 3 was compared. Reduced intake on day 3 indicates a conditioned taste aversion due to illness induced by drug treatment on day 1. LiCl treatment (127mg/kg; IP) was used as a positive control. The results of Fig. 6 illustrates that 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4'-Cl)-Arg-Trp-NH_2, administered IP at 1500 µg/kg, did not induce

a conditioned taste aversion response, illustrating that the decreased food intake in Figs. 4 and 5 was not due to aversive effect of 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4'-Cl)-Arg-Trp-NH_2.

Each of the foregoing is merely illustrative, and other equivalent embodiments are possible and contemplated.

Although this invention has been described with reference to these preferred embodiments, other embodiments can achieve the same results. Variations and modifications of the present invention will be obvious to those skilled in the art and it is intended to cover in the appended claims all such modifications and equivalents. The entire disclosures of all applications, patents, and publications cited above are hereby incorporated by reference.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.